REMARKS

Claims 99, 100, 102-104 and 107-115 are pending after entry of this paper. Claims 99-104 have been rejected. Claims 107-115 have been withdrawn and claims 1-98, 101, 105, and 106 have been cancelled without prejudice. Applicants reserve the right to pursue withdrawn and cancelled claims in a divisional or continuing application.

Claims 99, 100 and 102 have been amended.

Claims 100 and 102 have been amended to replace the term "agent" with the term "antibody." Support for this amendment may be found throughout the originally filed specification. (See, e.g., original claims 34 and 42 and at page 21, lines 34 - 37 of the instant specification).

No new matter has been introduced by these amendments. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Also enclosed herein for further support is a Declaration under 37 C.F.R. §1.132 from Professor Ugur Sahin, M.D. ("the Sahin Declaration").

Response to 35 U.S.C. §112 Rejection, First Paragraph- Enablement

Claims 99-104 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the enablement requirement. Specifically, the Examiner contends that the claimed method for diagnosing stomach cancer is not enabled by the specification. Applicants respectfully disagree. However, in order to expedite prosecution without disclaimer of, or prejudice to, the subject matter recited in the

instant application, applicants have amended the claims. Specifically, claim 99 has been amended to delete recitation of a methodology of diagnosing stomach cancer.

The Examiner has maintained his allegation that there is no predictable correlation in general between mRNA and protein expression. Thus, the Examiner is of the opinion that it cannot be predicted that the expression of Claudin-18A2 mRNA in pancreatic and esophageal cancers is correlated with Claudin-18A2 protein (SEQ ID NO: 16) expression absent direct empirical evidence showing expression of Claudin-18A2 protein (SEQ ID NO: 16) in pancreatic and esophageal cancers (Office Action, page 4). Applicants respectfully disagree with the Examiner's contention.

The applicants assert that diagnosing pancreatic and/or esophageal cancer by the method of claim 99 is enabled by the instant specification. The subject application as filed clearly identifies Claudin-18A2 mRNA as being expressed in association with tumors, e.g., pancreas carcinoma and esophageal carcinoma, and not expressed in normal tissue, e.g., pancreas or esophagus tissue (*see*: Table 3a of the patent application as filed). For example, the presence of Claudin-18A2 mRNA has been correlated with the presence of Claudin-18A2 protein (SEQ ID NO: 16) in lung carcinoma tissue (*see*: FIG. 24). Thus, the originally filed speciation enables a method according to claim 99 in the case of Claudin-18A2 since the presence of the mRNA is indicative of the presence of the corresponding protein.

The Examiner alleges that protein expression cannot be predicted based on RNA expression data and cites for support of this statement Greenbaum et al. (2003, *Genome Biology* 4:117.1-117.8), Brennan et al. (1989, J. *Autoimmunity* 2 (suppl.): 177-186), Zimmer (1991, *Cell Motility and the Cytoskeleton* 20:325-337), Hell et al. (1995,

Laboratory Investigation 73:492-496), Fu et al. (1996, *EMBO J.* 15:4392-4401), Vallejo et al. (2000, *Biochimie* 82:1129-1133), and Jang et al. (1997, *Clinical Exp. Metastasis* 15:469-483); see pages 12 to 14 of the Office Action dated October 17, 2006; page 4, 2nd paragraph of the Office Action dated June 6, 2007; page 4, 2nd paragraph of the Office Action dated February 14, 2008. In contrast to the Examiner's allegations, analysis of the cited documents shows that the majority of the cited references actually support that the presence or absence of mRNA is indicative of the presence or absence of protein, respectively (*see*: the Sahin Declaration, pages 3-5). Applicants submit herewith the Declaration of Professor Ugur Sahin, M.D. ("the Sahin Declaration") to address each of the Examiner's citations.

Greenbaum et al. found in all instances that there is a positive mRNA-protein abundance correlation for ORFs studied. While Greenbaum et al. studied a quantitative correlation of mRNA with protein amounts, the instant patent application teaches a positive correlation between the presence of mRNA with the presence of the corresponding protein, that is, the presence of mRNA indicates the presence of protein, while the absence of mRNA indicates the absence of protein. Thus, in the instant application, it is only the absence or presence of mRNA that should be indicative of the absence or presence of protein without regard to any quantitative correlation (*see*: the Sahin Declaration, page 3, point 5.1).

Brennan et al. report an example where mRNA levels are high, and the respective proteins were not detected. However, Brennan et al. note with respect to this phenomenon that "more sensitive assays are clearly needed to explore this further"; *see*: page 182. Furthermore, since this publication is almost 20 years old, it appears

that the apparent absence of protein is rather due to the insensitivity of the assay than due to an actual absence of protein (*see*: the Sahin Declaration, page 4, point 5.2).

Zimmer observes that while the distribution of certain mRNAs paralleled the protein distribution in all muscles, there was no direct correlation between the mRNA and protein levels in different muscle types; see abstract. Thus, Zimmer clearly observes that the presence of mRNA is indicative for the presence of protein, i.e., qualitatively (*see*: the Sahin Declaration, page 4, point 5.3).

Hell et al. describe a study on the expression of a specific gene relevant to Hodgkin's disease both at the protein and mRNA level. According to the results of the study, it appears that, while protein levels may vary, the presence of mRNA is indicative for the presence of protein in the study (*see*: the Sahin Declaration, page 4, point 5.4).

Fu et al. report on a study on translational regulation of gene expression and find that while mRNA was present in all samples examined, the expression of the corresponding protein was variable from patient to patient. However, the studied transcription factor belongs to the category of *regulatory proteins*. Applicants submit herewith a reference by Guo et al. (2008, *Acta Biochim Biophys Sin* 40:426-436), which shows that genes belonging to this category of regulation had non-significant and lowest mRNA protein expression correlations (*see*: e.g., abstract of Guo et al.). With respect to the claimed method, Claudin-18A2 is not a regulatory but rather is a *structural* protein. Thus, the phenomenon observed for by Fu et al. cannot be applied to Claudin-18A2, in particular, especially since it has been shown in the above patent application that presence of Claudin-18A2 mRNA indicates the presence of Claudin-18A2 protein, e.g.,

lung cancer (*see*: the Sahin Declaration, pages 4 and 5, point 5.5 and FIG 24 of the application as filed).

Vallejo et al. have analyzed the expression of NRF-2 both at the mRNA and at the protein level and have found no correlation between NRF-2 mRNA and protein levels; see abstract. However, they clearly show that all samples do express NRF-2 protein. Thus, the presence of mRNA is indicative for the presence protein; *see*: Figure 1 and Table I. Furthermore, Vallejo et al. also show that there is perfect correlation between the mRNA and protein levels for Tfam and β-actin; (*see*: Vallejo Figure 2 and Table I) (*see*: the Sahin Declaration, page 5, point 5.6).

It appears that Jang et al. have not studied the correlation of mRNA and protein levels, since they state that further studies are required to establish whether changes in protein levels track with changes in mRNA levels for the investigated genes; *see*: abstract. Thus, Jang et al. cannot serve to substantiate the Examiner's argument. (*see*: the Sahin Declaration, page 5, point 5.7).

The Sahin declaration describes that there is a consensus opinion in the field that even though the amount of mRNA may not reflect the amount of protein present in a cell, presence of mRNA is generally also indicative for presence of protein (*see*: the Sahin Declaration, page 5, point 6 through point 6.4). In the Sahin Declaration, Dr. Sahin provides support that it was, and still currently is, known in the field that the presence of mRNA is indicative for the presence of protein. (*see*: Tian et al. (2004, Molecular & Cellular Proteomics 3:960-969); Shankavaram et al. (2007, Mol. Cancer Ther. 6:820-832); Orntoft et al. (2002, Molecular & Cellular Proteomics 1:37-45); and Guo et al. (2008, Acta Biochim. Biophys. Sin. 40:426-436); attached herewith)

Furthermore, genes of structural proteins, such as Claudin-18A2, are regulated by transcription rather than by translation. Thus, higher mRNA-protein correlation coefficients are generally observed for such proteins (*see*: the Sahin Declaration, page 7, Summary).

In view of the fact that (i) Claudin-18A2 mRNA is not present at all in normal tissues except testis and stomach but is present in considerable amounts in several cancer types, (ii) there is no indication for a missing correlation between Claudin-18A2 mRNA and protein expression and (iii) a positive correlation between Claudin-18A2 mRNA and protein expression for normal lung tissue and lung cancer tissue, respectively, has been demonstrated in the above patent application, it is evident that Claudin-18A2 protein is a useful marker in the diagnosis of cancer for which presence of Claudin-18A2 mRNA is characteristic (*see*: the Sahin Declaration, page 7, Summary).

Applicants respectfully assert that one skilled in the art reading the instant specification in conjunction with common knowledge in the art would understand that the presence of Claudin-18A2 mRNA would be indicative of the presence of Claudin-18A2 protein of SEQ ID NO: 16.

Applicants respectfully assert that claims 99, 100, and 102-104 are sufficiently enabled by the specification. Reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph, enablement rejections are respectfully requested.

Response to 35 U.S.C. §112 Rejection, First Paragraph- Written Description

Claims 99-104 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Specifically, the

Examiner contends that the applicants were not in possession of a genus of "binding agents" at the time the invention was filed. Applicants respectfully disagree. However, in order to expedite prosecution without disclaimer of, or prejudice to, the subject matter recited in the instant application, applicants have amended the claims to incorporate the subject matter of previously presented claim 101. Specifically applicants have amended claims 100 and 102 to replace the term "agent" with "antibody." The amended claims are now directed to a well described genus.

Applicants respectfully assert that the instant specification provides an adequate written description so that one skilled in the art would understand that the applicants had possession of the claimed invention at the time that the instant application was filed. Thus, applicants respectfully request reconsideration and withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph to claims 99, 100, and 102-104 in view of the above-mentioned claim amendments.

Dependent Claims

Applicants have not independently addressed all of the rejections of the dependent claims. Applicants submit that for at least similar reasons as to why independent claim 99 from which all of the dependent claims 100, and 102-104 depend are believed allowable as discussed *supra*, the dependent claims are also allowable. However, applicants reserve the right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable and respectfully request that the respective rejections be withdrawn.

CONCLUSION

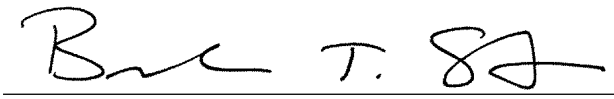
Based on the foregoing amendments and remarks, the applicants respectfully request reconsideration and withdrawal of the pending rejections and allowance of this application. The applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4883-0001.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4883-0001.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: July 14, 2008 By: 

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